REMARKS/ARGUMENTS

I. Status of the Claims:

Claims 31, 32, 35-37, 39-41 and 43-69 and 72-78 are pending in the application, with claims 45-63 withdrawn as directed to a non-elected invention. Upon entry of this amendment, claims 31, 65, 68, 69, 75 and 77 are amended, and claims 45-63 and 67 canceled, without prejudice or disclaimer. Claims 45-63 are canceled solely because they have been withdrawn as directed to a non-elected invention. Thus, claims 31, 32, 35-37, 39-41, 43-44, 64-66. 68-69, and 72-78 are pending following entry of this amendment.

Claim 31 has simply been amended to correspond with original claim 75. The amendment to claim 75 is supported, for example, at page 5, penultimate paragraph.

II. Claim Rejections under 35 U.S.C. § 102:

A. Burnouf-Radosevich Distinguished

Claims 31-32, 35-37, 39-40, 43-44, 66-69 and 72-73 are rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,408,039 to Burnouf-Radosevich ("Burnouf-Radosevich"). The basic argument made in the Office Action is that while Burnouf-Radosevich discusses methods for generating high purity vWF compositions these compositions may nonetheless contain trace amounts of propeptide and/or pro-vWF. Reference to a "pharmaceutically effective amount" was said not to be adequately defined in the specification such that it distinguished any very low level of propeptide or pro-vWF that might be present in the compositions discussed by Burnouf-Radosevich.

Although Applicants do not agree with this analysis for the reasons described at length in the preceding responses, in the interest of advancing prosecution of important subject matter, the two independent claims rejected over Burnouf-Radosevich, i.e., claims 1 and 64, have respectively been amended and canceled. Independent claim 1, for instance, which is directed to pro-peptide compositions has been amended to recite that the composition comprises at least 10

nM pro-peptide. Claim 1, then, replaces claim 75, a claim which the Office indicated to be patentable over Burnouf-Radosevich. Claim 67, which recites to compositions comprising pro-vWF, has been canceled and claims 68 and 69, previously dependent upon claim 67, amended to depend from claim 77, which the Office has also indicated to distinguish over Burnouf-Radosevich.

B. Takagi Distinguished

Claims 31-32, 39-40, 43-44, 64-65, 72 and 74-76 are rejected as anticipated by Takagi et al. (Takagi et al. (J. Biol. Chem. (1989) 264:6017-6020). The Office Action says that Takagi discusses compositions that comprise vWF pro-peptide from human platelets at concentrations greater than 50 nM. The Office says that the burden is on the Applicants to prove that the Takagi compositions do not contain viruses. The Office thus presumes that Takagi anticipates the foregoing claims absent evidence to the contrary.

In response, Applicants point out that the compositions discussed by Takagi were prepared from human platelets. Because blood samples can potentially be contaminated with viruses, health authorities require an appropriate virus inactivation or virus removal step for approval of any pharmaceutical preparation derived from blood. The preparations discussed by Takagi were not treated with any virus removal or virus inactivation step as required by the claims. Thus, Takagi fails to anticipate the claims.

Claim 72 further distinguishes Takagi. This claim requires that the pro-peptide composition is suitable for parenteral administration. As indicated in the enclosed copy (Attachment A) of the Introduction from a chapter entitled "Dosage Forms: Parenterals" by Brazeau et al. in the "Encyclopedia of Pharmaceutical Technology" (Swarbrick et al., eds., 2nd Ed., Marcel Dekker, 2002), parenteral products are "prepared scrupulously by methods designed to ensure that they meet pharmacopeial requirements for sterility, pyrogens, particulate matter, and other contaminants." It is clear, however, that the compositions discussed in Takagi were prepared simply for use in routine laboratory experiments, not under the "scrupulous" conditions

necessary to obtain a preparation having a composition suitable for parenteral administration. Thus, the preparations of claim 72 are further distinguished over Takagi on this basis.

III. Rejections under 35 U.S.C. § 103(a):

Claims 31, 32, 39, 40, 43-44, 64-65 and 72 are rejected under 35 U.S.C. § 103(a) as obvious over an article by Takagi et al. (J. Biol. Chem. 264:6017-6020, 1989; hereinafter "Takagi") in view of EP 131740 to Neurath (hereinafter "Neurath") and an article by Blann et al. (Eur. J. Vasc. Surg. 8:10-15, 1994; hereinafter "Blann").

The Office continues to take the position that Takagi discloses a composition containing purified vWF-propeptide. Although it is acknowledged that Takagi does not teach or suggest vWF-propeptide compositions that have been treated for at least one of viral inactivation or virus removal and that are suitable for therapeutic administration, Neurath is said to discuss methods for making compositions that are free of certain viruses. The combined discloses of Takagi and Neurath is thus said to render the foregoing claims obvious.

The motivation for making the combination is said to be found in the combined discussion of Takagi and Blann. Blann is said to discuss how increased vWF levels are correlated with various risk factors for atherosclerosis and arterial disease. The Office Action also states that Blann suggests that in view of such correlations that future therapies for treating atherosclerosis and arterial disease might use agents that inhibit vWF activity. Since Takagi is said to discuss the possibility that vWF-propeptide might have an effect on hemostasis that opposes that of mature vWF (e.g., inhibition of collagen-induced aggregation of human platelets), the Office Action concludes that one of skill in the art would have been motivated to combine the purified vWF-propeptide compositions of Takagi with the viral inactivation methods of Neurath to obtain pharmaceutical compositions useful in treating individuals at risk for atherosclerosis or arterial disease because of elevated vWF levels. For the reasons that follow, Applicants respectfully disagree.

A. No Motivation to Combine the Cited References

As emphasized in the last response, the Office is obligated to provide "evidence of the motivating force that *impels* one skilled in the art to do what the patent applicant has done (Ex parte Levengood, 28 USPQ2d 1300, 1302 (Bd. Pat. App. & Inter. 1993) (emphasis added). As just noted, the Office Action contends that the requisite motivation is provided by the discussion in Blann indicating a need for preparations that oppose the negative effects on arteries associated with elevated vWF levels and the discussion in Takagi indicating that vWF-propeptide and mature vWF might have opposing effects with respect to platelet adhesion to the subendothelium of arteries.

But as pointed out in the last response, this rationale presumes that Blann teaches that vWF is a *causative agent* in atherosclerosis or other arterial diseases. Applicants, however, explained at length in the last response that Blann did not support such a conclusion. The Office disagrees stating, for example, that Blann emphasizes that vWF levels were raised in patients with atherosclerosis. But as pointed out in the last response, it does not follow that this necessarily means that vWF is a causative factor. An at least equally likely explanation is that it is simply a marker.

The Office also contends that Blann "repeatedly suggests that high levels of vWF *might* predispose to or promote atherosclerosis . . . and that reducing vWF levels *might be a future* therapeutic" (Office Action at page 15; emphasis added). In making this statement, the Office itself admits that Blann is at best speculating about a potential correlation and possible future developments. Such speculation falls well short of a motivating force that *impels* one skilled in the art to do what the patent applicant has done as required to establish a prima facie case of obviousness.

With respect to Blann's statement that "[h]ence there is no data in humans which would allow us to conclude that von Willebrand disease [i.e., low vWF levels] protects from atherosclerosis (Blann at page 13, column 1, last sentence of the first full paragraph), the Office says that this should not be read to imply that Blann concludes that vWF is not a causative factor

of atherosclerosis. Instead, the Office says that Blann is simply stating that due to the complexity of von Willebrand disease and due to the added complexity of its treatment with vWF and factors that induce vWF release, that von Willebrand disease cannot be used as a model for low vWF.

There are, however, several difficulties with this analysis. First, the section from page 13 of Blann that the Office cites to is not a section in which Blann "suggests" that there is a correlation between high vWF levels and atherosclerosis as the Office implies, rather Blann speaks in hypothetical terms, saying: "If it is the case that high levels of vWf somehow predispose to, or promote atherosclerosis, then low levels should be protective against the disease." This statement does not rise to the level of a suggestion, it is rather a speculative statement. Worse yet for the Office's position, the results of investigations with von Willebrand patients that could potentially answer this question indicated that vWF was not a causative factor. Although the Office proposes that this negative result is simply because vWF patients are a poor model system, the key point is that there is nothing in this section upon which the Office relies that provides the requisite motivation. Instead, this section simply hypothesizes about a correlation that the Office presumes to exist and presents results contrary to the Office's position.

Moreover, irrespective of the interpretation of this particular section of Blann, the Office has not dealt with the two overall conclusions in Blann, namely that:

> "There is clearly more scope for studies which seek to explain raised levels of vWf and their association with disease." (Blann, at page 13, column 1, last two lines); and
>
> "It *may* be that *future studies* will recommend that the aim of clinical treatment be reduction in vWf levels and so may be the object of novel therapeutic approaches." (Blann, at page 13, column 2, last paragraph).

As pointed out in the last response, it is clear from these statements that Blann considered there to be insufficient evidence to support the hypothesis that a reduction of vWF levels could convey a therapeutic effect. Rather the clear implication from the foregoing statements is that Blann was of the view that only after additional work had been completed would it be possible to ascertain whether vWF levels could be used in therapeutic methods. This falls well short of a motivation that would *impel* one to develop the currently claimed invention.

Finally, the Office in its analysis does not address the surprising new pharmacological function of vWF propeptide recognized by the inventors, namely the stimulating effect on thrombin generation. This effect is neither taught or suggested in the cited references. Thus, contrary to the view taken by the Office, vWF propeptide is not simply an antagonist that can bind to a collagen surface, but rather it plays another important role in the balanced regulation of the whole coagulation procedure.

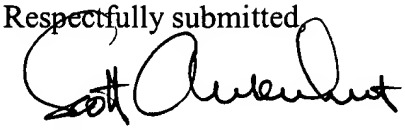
IV. Claim Rejections under 35 U.S.C. 112, First Paragraph

Claims 77 and 78 are rejected because the specification is said not to describe how to obtain pro-vWF solutions that contain at least 10 nM or at least 100 nM pro-vWF.

In response, it is noted that the Turecek et al. (Blood (1999) 94:1637-1647) and Varadi et al. (Thromb. Haemost. (2001) 86:1449-1458) articles referred to by the Examiner in the Office Action, each reference back to earlier articles describing methods for purifying pro-vWF that published before the filing date of the instance application. The Turecek article, for example, at page 1638, column 1, penultimate paragraph, refers to an article by Fischer et al. (FEBS Lett. 351:345, 1994) and Megan et al. (Thromb. Haemost 59:364 (1998)]. The Varadi article, for example, at page 1449, last paragraph, refers back to the same articles. The methods described in these earlier articles could have been utilized to prepare compositions having at least 10 or 100 nM pro-vWF.

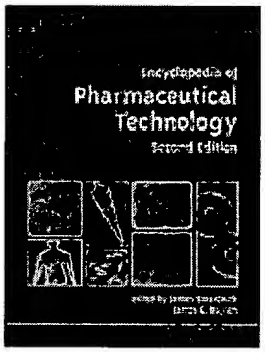
If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 303-571-4000.

Respectfully submitted,



Scott L. Ausenhus
Reg. No. 42,271

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: 303-571-4000
Fax: 415-576-0300
SLA:tnd
47103417 v2



Dosage Forms: Parenterals

Published in Encyclopedia of Pharmaceutical Technology
ISBN: 0-8247-2826-2

Gayle A. Brazeau [1]
Adam Persky [1]
Jintana M. Napaporn [1]
[1] *University of Florida*
Gainesville, Florida, U.S.A.

Encyclopedia Entry | Print Published: 05/22/2002 | Online Published: 01/23/2002
Pages: 762 - 773 | PDF File Size: 183 KB
DOI: 10.1081/E-EPT-100001047

Introduction

Parenteral is derived from the two words "para" and "enteron" meaning to avoid the intestine. Parenteral articles are defined according to the USP 24/NF19 "as those preparations intended for injection through the skin or other external boundary tissue, rather than through the alimentary canal, so that the active substances they contain are

administered using gravity or force directly into a blood vessel, organ, tissue, or lesion. Parenteral products are prepared scrupulously by methods designed to ensure that they meet pharmacopeial requirements for sterility, pyrogens, particulate matter, and other contaminants, and, where appropriate, contain inhibitors of growth of microorganisms. An injection is a preparation intended for parenteral administration and/or for constituting or diluting a parenteral article prior to administration" (1). Parenteral drug administration is an attractive route of administration when oral administration is contraindicated, and it has been traditionally used in institutional settings. With an increasing interest in reducing overall health care costs and with the development of new biotechnologically derived compounds and improved and novel infusion-related technologies, parenteral products have become an important component in the care of patients in hospitals and the home health care setting. In the present article, information will be presented on history and the following: the use of parenterals in health care, the advantages and disadvantages of using parenterals, routes of administration, vascular access devices and infusion sets, types of parenteral products, components of parenteral products, parenteral packaging, convenience and needleless systems, needleless injection, extemporaneous compounding of parenteral products, infusion pumps and devices, and future parenteral dosage forms.

Return to Top